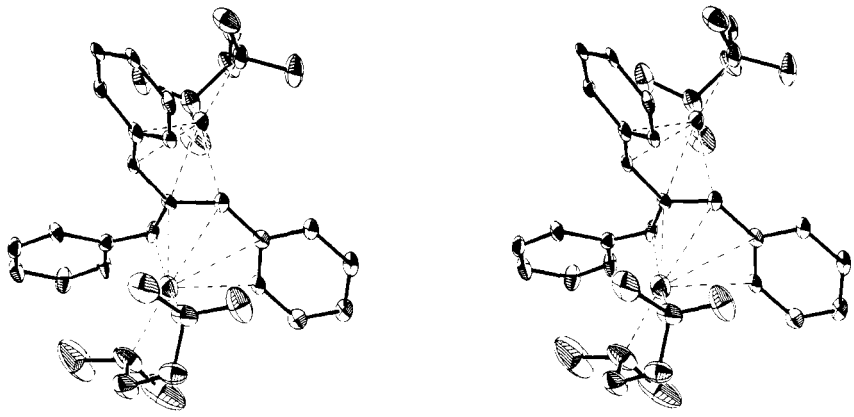

Figure 1. Stereoplot of the X-ray structure of dilithium tribenzylidenemethane–2TMEDA.

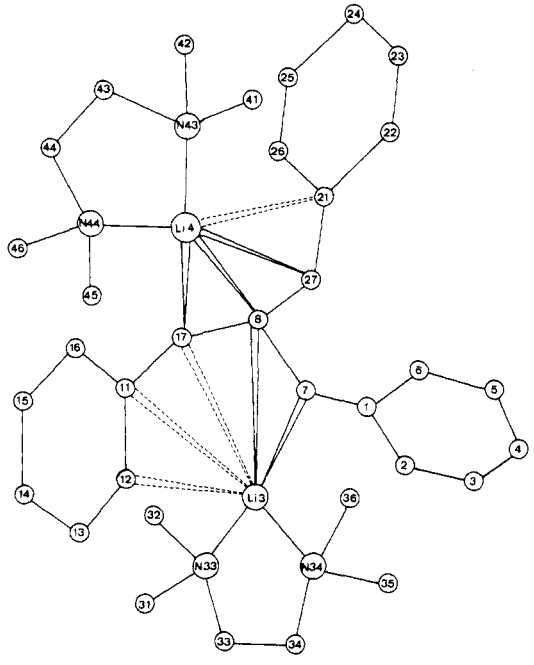

Figure 2. Schematic view of the structure in Figure 1. Important bond lengths in Å: C(8)–C(27) 1.460 (3), C(8)–C(17) 1.443 (3), C(8)–C(7) 1.388 (4), C(11)–C(17) 1.441 (3), C(7)–C(1) 1.420 (3), C(27)–C(21) 1.434 (4), Li(4)–C(21) 2.667 (4), Li(4)–C(27) 2.234 (5), Li(4)–C(8) 2.287 (6), Li(4)–C(17) 2.304 (5), Li(3)–C(7) 2.297 (5), Li(3)–C(8) 2.337 (6), Li(3)–C(17) 2.626 (6), Li(3)–C(11) 2.784 (6), Li(3)–C(12) 2.673 (5), C(1)–C(2) 1.395 (4), C(2)–C(3) 1.372 (4), C(3)–C(4) 1.437 (3), C(4)–C(5) 1.369 (4), C(5)–C(6) 1.371 (4), C(1)–C(6) 1.462 (3). Lithium–nitrogen distances vary between 2.025 and 2.118 Å.

dianion[12] and confirms this interpretation. The phenyl groups are twisted from the trimethylenemethane plane, as suggested by MNDO calculations on the dianion.[3] The entire structure, with lithium atoms above and below the dianion plane in bridging positions between the carbon atoms with the highest negative charges, is electrostatically very favorable. The quinonoid distortions of the phenyl substituents (indicative of delocalization of the negative charge) are most pronounced for the ring bound to C(7), although the differences are not large. Finally, we note that the orientation of the TMEDA ligand coordinated to Li(4) is that expected from Stucky's orbital arguments[5,12] but that the orientation of the other diamine moiety is consistent with an interaction with C(7) and C(12).[13]

The X-ray structure of a related Y-conjugated 1,3-acetone "dianion" derivative (dilithiated dibenzyl ketone) has just been reported.[14] We have now been able to obtain the X-ray structure of another Y-conjugated system, dilithium dibenzylidinethylene–2-tetramethylpropanediamine.[15] The geometry resembles **5** more closely than does **2**.

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Registry No. 1, 13001-05-3; **2**, 92314-26-6.

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(13) See Bushby et al. (Bushby, R. J.; Tytko, M. P. *J. Organomet. Chem.* **1984**, *270*, 265) for an electrostatic interpretation of lithiated π-carbanion structures.
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^{13}C, ^{1}H, and ^{2}H NMR Observation of Trideuterated Cyclopropylmethyl–Cyclobutyl Carbocation: A Configurationally Stable Species[1a]

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With the increasing power and sophistication of experimental and theoretical methods for assigning chemical structures, it seems almost incredible that the structure of any reasonably stable organic entity with a small number of carbons could remain enigmatic for very long. Nonetheless, this is true of $C_4H_7^+$—one of the first "nonclassical" cations to be discovered, which has some of the characteristics expected for a very rapidly equilibrating mixture of classical cyclopropylmethyl, cyclobutyl, and 3-butenyl cations and yet other characteristics which wholly belie any description that implies conventional charge distriutions or geometries derived from structural representations using solid lines representing two-electron bonds.[2]

(1) (a) Supported by the National Science Foundation. (b) NSF Fellow, 1979–1980.
(2) Staral, J. S.; Roberts, J. D.; Prakash, E. K. S.; Donovan, D. J.; Olah, G. A. *J. Am. Chem. Soc.* **1978**, *100*, 8016, 8018.

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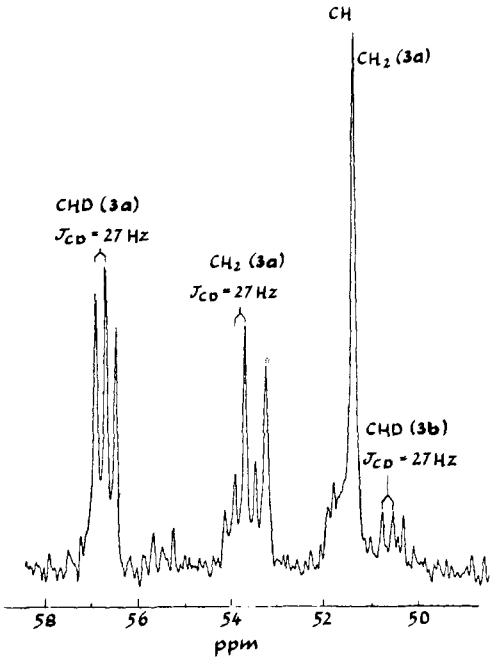
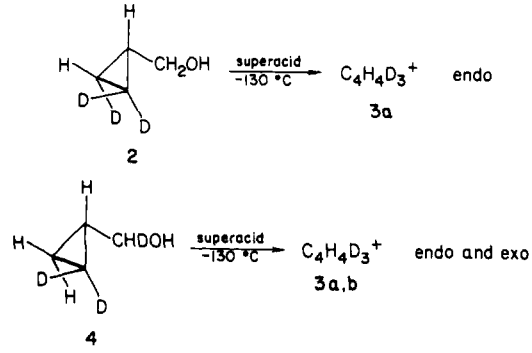


Figure 1. Methylene-shift region of the proton-decoupled 125.7-MHz ^{13}C FT NMR spectrum of *endo*-$C_4H_4D_3^+$ (**3a**) at -95 °C in SbF_5–SO_2ClF–SO_2F_2 solution. (* corresponds to an unknown resonance.)

Further evidence bearing on the nature of $C_4H_4D_3^+$ in SbF_5–SO_2ClF–SO_2F_2 ("superacid")[3] has been obtained from ^{13}C, ^1H, and ^2H NMR spectroscopy[4] at temperatures ranging from -121 to -80 °C. Specifically, (2*E*)-, (2*Z*)-, (3*E*-cyclopropyl-d_3)methanol (**2**)[5] affords a long-lived, quite stereochemically stable $C_4H_4D_3^+$ species (**3a**), while (cyclopropyl-2,2-d_2)methan-*d*-ol (**4**),[6] under the same conditions, produces **3a** and its stereoisomeric species **3b**. These stereoisomeric species, the likelihood of which



was earlier recognized by Saunders and Siehl,[7] will be here designated as endo (**3a**) and exo (**3b**), although it is abundantly clear from earlier studies[2,7] that they are very rapidly equilibrating mixtures of $C_4H_4D_3^+$.

Figure 1 shows the three nonequivalent methylene resonances of the 125.7-MHz ^{13}C NMR spectrum of **3a** at -95 °C, each of which can be identified by its $^1J_{CD}$ splitting pattern. Smaller peaks

(3) Olah, G. A.; Kelly, D. P.; Jeuell, C. H.; Porter, R. D. *J. Am. Chem. Soc.* **1970**, *92*, 2544; **1972**, *94*, 146.

(4) Chemical shifts are relative to external tetramethylsilane and are accurate to ±0.01 ppm for carbon and ±0.001 ppm for deuterium and hydrogen. For complete experimental details, see: Brittain, W. J. Ph.D. Dissertation, California Institute of Technology, Pasadena, CA, 1982.

(5) Prepared by lithium aluminum hydride reduction of the corresponding carboxylic acid; see: Kobayashi, K.; Lambert, J. B. *J. Org. Chem.* **1972**, *42*, 1254.

(6) Synthesized starting from prop-2-en-1-al. Protection of the carbonyl, cyclopropanation with CD_2N_2, vacuum pyrolysis of pyrazolines, deprotection, and lithium aluminum deuteride reduction gave a mixture of deuterated 3-butenyl and cyclopropylmethyl alcohols which could easily be separated by preparative gas chromatography.

(7) Saunders, M.; Siehl, H. *J. Am. Chem. Soc.* **1980**, *102*, 6868–6869.

Table I. ^{13}C Chemical Shifts (ppm/Me_4Si) Assigned to $C_4H_4D_3^+$ (**3a** and **3b**) at −95 °C

	$^{13}CH_2$	^{13}CHD	$^{13}CD_2$	^{13}CH
3a	51.35	56.69	53.68	109.81
3b	53.68	50.51	55.70	110.28

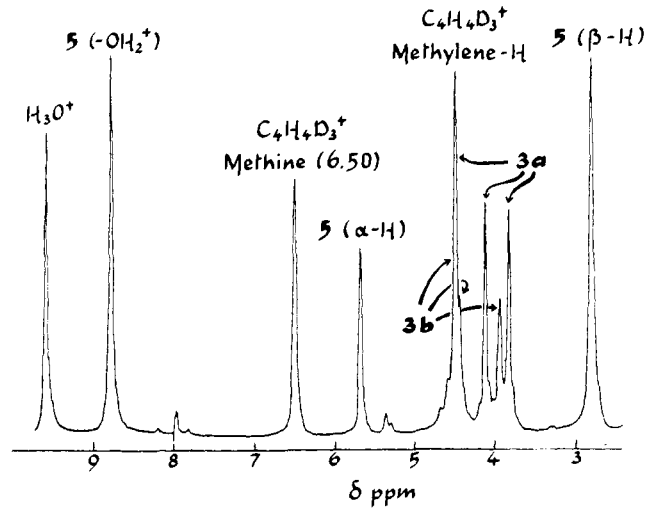


Figure 2. FT 500-MHz ^1H NMR spectrum of **3a** containing some **3b**, at -121 °C in SbF_5–SO_2ClF–SO_2F_2 solution; the proton resonances assigned to cyclobutyloxonium ion (**5**) are so labeled. The methylene proton resonances (in ppm): **3a**, 4.49, 4.12, 3.83; **3b**, 4.49, 4.44, 3.94.

(Figure 1) arising from the stereoisomer **3b** could be identified by comparison with the corresponding equimolar mixture of **3a** and **3b** prepared from **4**. Still other peaks correspond to cyclobutyloxonium ion (**5**).[2]

The pattern of ^{13}C shift differences between **3a** and **3b**, as well as between these moieties and the shifts[3] for $C_4H_7^+$ (**1**) is quite striking. Relative to the corresponding ^{13}C resonances of **1** as internal standard, the following are the ^{13}C shifts, in ppm at -94 °C, of **3a** and **3b**, respectively: (CH_2) -3.0, -0.7; (CHD) 2.2, -3.6; (CD_2) -0.8, 1.0 (?);[8] (CH) 0.0, 0.4. Whatever else can be said about these shifts, the influence of the endo–exo configuration at the CHD carbon is indeed significant (Table I).

In the 500-MHz ^1H spectrum of **3a** (admixed with some **3b**) shown in Figure 2, the *endo*-methylene protons (the protons trans to the methine) have chemical shifts more toward lower fields (4.64 ppm[3]) than do the *exo*-methylene protons (4.21 ppm[3]). This suggests different shift assignments than derived previously.[3] Several 76.7-MHz ^2H NMR spectra of $C_4H_4D_3^+$ samples prepared from **2** and **4** were taken to assess the extent of deuterium migration from methylene to the methine position. Even after extended periods above -80 °C, no ^2H resonance was observed in the methine region.

Conversion of **3a** to **3b** was not clearly observed at -90 °C in 4 h. The outside limit of reaction was about 12%, which would correspond to a lower limit for the free energy of activation of around 14 kcal/mol. This, then, must be the lower limit for the free energy of $C_4H_7^+$, either for conversion to the planar cyclobutyl cation or for rotation about a methylene to methine carbon–carbon bond. This fact, along with the small isotopic perturbations of the ^{13}C chemcial shifts reported here and by Saunders and Siehl[7] provide compelling evidence that $C_4H_7^+$ cannot be regarded as a rapidly equilibrating mixture of *classical* cations.

The remarkable difference in the direction of the isotope shifts in the ^{13}C resonances of **3a** and **3b** and the much larger isotopic perturbations of the exo-proton shifts compared to the endo-proton shifts (Figure 2) indicates that one or more of the equilibrating structures of $C_4H_7^+$ must have an *exo*-methylene proton located in a unique environment compared to the other protons. If the

(8) Uncertain because of poor signal-to-noise ratio and overlap with the resonances of $C_4H_7^+$, which was present in the solution as internal standard.

particular $C_4H_7^+$ structure has a pentacoordinated carbon with the elements of square-pyramidal geometry and possesses an *exo*-methylene proton at the apical position, this could account for the observed isotopic perturbations. The bicyclobutonium cation structure has a pentacoordinated carbon which could possess this configuration.

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Estrogen Biosynthesis. Concerning the Obligatory Intermediacy of 2β-Hydroxy-10β-formylandrost-4-ene-3,17-dione

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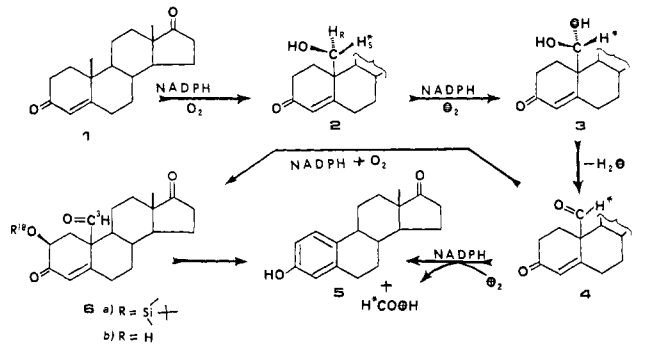
The transformation of an androgen (**1**) to an estrogen (**5**) by human placental aromatase was shown to involve three oxidative steps, each of which requires 1 mol of O_2 and 1 mol of NADPH.[1] The process is initiated by C-19 hydroxylation[2,3] (**2**) in the retention mode[4] and is followed by the introduction of a second C-19 hydroxyl[5] (**3**). The second hydroxylation proceeds with the stereospecific abstraction of 19-*pro-R* hydrogen atom of the 19-alcohol[6-8] **2**. The obtained diol **3** is then dehydrated with the loss of the "second" hydroxyl[9] to give the 19-aldehyde **4**. The aldehyde is subsequently aromatized with the consumption of a (third) mole each of oxygen and NADPH, and C-19 is extruded as formic acid.[5,9]

Fishman et al.[10-13] proposed that the "third" mole of oxygen and of NADPH are utilized for the enzymatic 2β-hydroxylation of a 19-aldehyde intermediate to give, e.g., 2β-hydroxy-10β-formylandrost-4-ene-3,17-dione (**6b**) (Scheme I). They proved

Scheme I



Scheme II

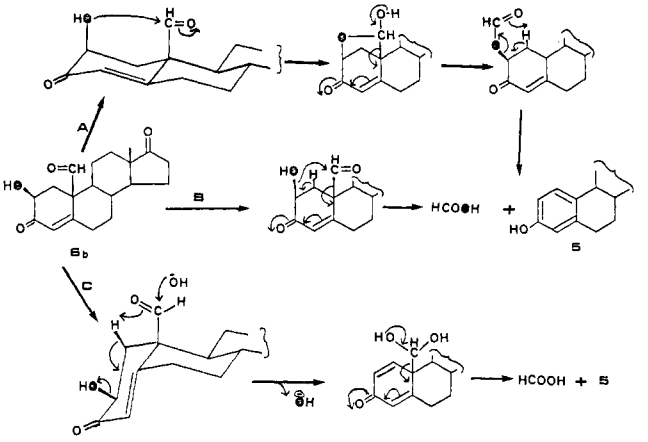


Table I. Aromatization of [2β-^{18}O,19-^{3}H]-2β-hydroxy-10β-formylandrost-4-ene-3,17-dione (**6b**): GC-MS Analyses of the Derived Benzyl Formates

source of $HCOOCH_2C_6H_5$	relative intensities of M^+ ions		
	m/z 136	*m/z* 137	*m/z* 138
(1) authentic, ref	100	9.2	0.94
(2) nonenzymatic[a] aromatization of **6b**	100	9.6	0.87
(3) enzymatic[a] aromatization of **6b**	100	11.6	0.94

[a] See text for details.

that the 2β-hydroxy-10β-formyl **6b** collapses nonenzymatically even at pH 7 with the loss of the 1β-hydrogen to give estrone and formic acid. On the basis of these and other observations,[10-13] they postulated that the last step of estrogen biosynthesis is the nonenzymatic aromatization of the presumably "not enzyme bound" **6b**. Accordingly they showed "that there is no end-product inhibition of aromatization by estrogens".[11]

The collapse of the 2β-hydroxy-10β-formyl **6b** can be rationalized in terms of the mechanisms (A, B, C) outlined in Scheme II. Pathway A provides for a "stepwise" aromatization of **6b**, while pathway B is a concerted process. It should be noted that according to mechanisms A and B, the oxygen atom of the 2β-hydroxyl of **6b** is incorporated into the formic acid produced in the aromatization process. In contrast, in mechanism C, the aromatization process is initiated by a hydroxyl group attack on the 10β-formyl moiety, and the oxygen of the 2β-hydroxyl group is eliminated as water.

Akhtar et al.[9] proved that the third mole of oxygen, required for completion of the aromatization process, is incorporated into the formic acid derived from C-19. It follows therefore that if **6b** is an *obligatory intermediate* in estrogen biosynthesis, the oxygen (e.g., ^{18}O) atom of the 2β-hydroxyl must be incorporated into the extruded formic acid, a point that was recognized by Hahn and Fishman.[13]

To test the Fishman et al. hypothesis, we have prepared [2β-^{18}O,19-^{3}H]-2β-hydroxy-10β-formylandrost-4-ene-3,17-dione 2-(*tert*-butyldimethylsilyl) ether[14] (**6a**). The mass spectrum showed

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